REMARKS/ARGUMENTS

Status of the Claims

Claims 12-19 were rejected. Claims 1-11 were withdrawn from consideration as being drawn to non-elected inventions and have been cancelled without prejudice or disclaimer. Applicants reserve the right to pursue these claims in a continuation or divisional application. Claims 12-13, 15-17, and 19 have been amended. Claims 12-19 are pending in the present application.

Amendments to the Claims

Claims 12-13, 15-17, and 19 have been amended to more clearly define the invention. Support for these amendments can be found throughout the specification and in the originally filed claims.

Claim 12 and its respective dependent claims have been further amended to recite "at least one filter." Support for this amendment can be found throughout the specification and in the originally filed claims. See, for example, page 6, lines 1-25 and page 8, lines 7-20. Claim 12 and claims dependent thereon have also been amended and now no longer recite "a combining means." Support for this amendment can be found throughout the specification. See, for example, page 11, lines 1-19. These amendments were made to clarify the claimed subject matter and do not narrow the scope of the claims.

No new matter has been added by way of these amendments. Reexamination and reconsideration of the claims, as amended, is requested.

The Objection to the Specification Should Be Withdrawn

The Examiner has objected to the use of trademarks in the application. The specification has been amended such that each trademark is followed by a proper trademark symbol, as required by MPEP 608.01(v). In light of these amendments to the specification, the objection has been obviated and should be withdrawn.

The Rejection of the Claims Under 35 U.S.C. § 112, Second Paragraph, Should Be Withdrawn

Claims 12-19 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. This rejection is respectfully traversed.

Claim 12 was rejected as indefinite for use of the term "aPEG." The Examiner is reminded that the definiteness of claim language is to be analyzed in light of the specification. MPEP § 2173.02. The term "aPEG" is expressly defined in the specification as "polyethylene glycol (PEG) and molecules related to PEG that have been activated so as to be capable of chemically modifying proteins, peptides, or other molecules" (page 4, lines 18-20). Thus, contrary to the Examiner's assertion, the term "aPEG" is not indefinite to one of skill in the art in light of the specification.

While claim 12 was not indefinite as originally submitted, the claim has been amended to further prosecution. Specifically, claim 12 has been amended in accordance with the Examiner's suggestion to recite "an activated polyethylene glycol (aPEG)" at the first use of the term. In light of this amendment, the rejection under 35 U.S.C. § 112, second paragraph, should be withdrawn.

Similarly, claim 13 was rejected as indefinite for use of the term "POE." Again, this abbreviation is not indefinite in light of the specification. The Examiner's attention is drawn to page 2, line 1, which clearly states that by "POE" is intended "the activated PEG molecule polyoxyethylene." Again, while claim 13 satisfies the requirements of 35 U.S.C. § 112, second paragraph, as originally submitted, the claim has been amended to further prosecution. In accordance with the Examiner's suggestion, claim 13 now recites "wherein the aPEG is polyoxyethylene (POE)." Therefore, the rejection should be withdrawn.

Claim 16 was rejected as vague for use of the abbreviation "EU." In contrast to the Examiner's assertion, the term "EU" is a standard unit of measure for quantitation of endotoxin levels and is commonly used in microbiology, and, thus, one of skill in the art would clearly

understand its meaning. Applicants maintain that the term "EU" is not indefinite, and, therefore, this rejection should be withdrawn.

Claim 12 was rejected for indefiniteness for use of the language "a chemically modified hemoglobin solution." Specifically, the Examiner asserts that it is unclear whether the solution or the hemoglobin is modified. The specification, however, clearly indicates that it is the hemoglobin which is chemically modified. For example, the Examiner's attention is drawn to page 4, lines 28-31, which states that the "aPEGs of the invention can be used to PEGylate any peptide or protein of interest" and indicates that in one preferred embodiment "the protein of interest is hemoglobin." Therefore, Applicants submit that claim 12, when read in view of the specification, would allow one of skill in the art to clearly understand the term "a chemically modified hemoglobin solution" to mean that the hemoglobin protein itself is chemically modified in the claimed methods. Consequently, the rejection under 35 U.S.C. § 112, second paragraph, should be withdrawn.

The Examiner further rejected claims 12 and 15 under 35 U.S.C. § 112, second paragraph, for use of the terms "substantially free of contaminants" and "substantially reduces endotoxin contaminant levels." Specifically, the Examiner maintains that it is unclear what level of contamination is permitted because "the term 'substantially' is a relative term which renders the metes and bounds of the claims indeterminate" (page 3, Office Action mailed July 1, 2003). The Examiner is reminded that the use of relative terminology such as "substantially" in a claim does not automatically render the claim indefinite. *Seattle Box Co. v. Industrial Crate & Packing, Inc.*, 731 F.2d 818, 221 USPQ 568 (Fed. Cir. 1984). Rather, the issue is whether one skilled in the art would understand what is claimed in light of the specification.

Here, the specification provides sufficient guidance to allow one of skill in the art to ascertain the metes and bounds of the claim limitations "substantially free" and "substantially reduces." For example, the specification provides specific percentages that represent substantial reductions in bacterial bioburden and endotoxin levels, as well as standard methods for determining these levels. See page 7, lines 11-28. Furthermore, the specification indicates that

hemoglobin and aPEG solutions that are substantially free of contaminants or have substantially reduced endotoxin levels are ones that are "noninfectious" (page 8, line 5) and are "characterized by not inducing pathophysiological effects characteristic of the presence of contaminants upon *in vivo* administration to a subject" (page 7, lines 30-31). Thus, contrary to the Examiner's assertions, given the significant guidance provided in the specification, one of skill in the art could ascertain the scope of claims 12 and 15. In light of the specification and above discussion, Applicants submit that claims 12 and 15 satisfy the requirements of 35 U.S.C. § 112, second paragraph, and, therefore, the rejection should be withdrawn.

The Examiner rejected claim 17 as indefinite for use of the language "micron micron." Applicants have amended claim 17 to correct this typographical error.

Claim 19 was rejected for indefiniteness for lack of antecedent basis for the term "combining means." Claims 12 and 19 have been amended and no longer recite "combining means." This amendment has obviated the rejection under 35 U.S.C. § 112, second paragraph.

Claim 17 was further rejected for indefiniteness for use of the trademark "Nylon 66 Posidyne" filter as a claim limitation. The claim has been amended and now recites only the generic term "nylon filter." In light of the claim amendment, this rejection has been obviated and should be withdrawn.

In view of the claim amendments and the above discussion, claims 12-19 particularly point out and distinctly claim the subject matter that Applicants regard as the invention. Accordingly, the rejection of the claims under 35 U.S.C. § 112, second paragraph, should be withdrawn.

The Rejection of the Claims Under 35 U.S.C. § 102 Should Be Withdrawn

Claims 12-16 and 18 were rejected under 35 U.S.C. § 102(b) as being anticipated by Talarico *et al.* (2000) *Biochim. Biophys. Acta* 1476: 53-65. This rejection is respectfully traversed.

Claims 12-19 are drawn to a method of preparing a chemically modified hemoglobin solution that is substantially free of contaminants comprising dissolving an activated aPEG in a solvent in which the aPEG is stabile, filtering the aPEG solution to substantially reduce the level of contaminants, and combining the filtered aPEG solution with a hemoglobin solution. Thus, the claimed methods require that the aPEG must first be dissolved in an appropriate solvent and then filtered before using the aPEG solution to chemically modify hemoglobin.

A prima facie case of anticipation under 35 U.S.C. § 102 has not been established. According to the Federal Circuit, "anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration." *W.L. Gore & Assocs. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983). Talarico *et al.* teach a method of producing a PEGylated hemoglobin composition comprising modifying a pyridoxalated stroma-free hemoglobin with an aPEG, followed by purification of the modified hemoglobin solution to remove residual reactants and contaminants. In contrast to the claimed method, the cited reference does not teach first dissolving the aPEG in a solvent in which it is stabile and then filtering the aPEG solution prior to combining it with the hemoglobin solution. In fact, the cited reference provides no guidance as to whether the aPEG is to be added to the hemoglobin fraction as a powder or as a solution. Rather, Talarico *et al.* merely state that "various molar excesses of PEG to pyridoxalated hemoglobin were reacted in buffer" (pages 54-55) and do not teach or suggest dissolving the aPEG in a solvent and filtering the aEPG solution prior to combining it with the hemoglobin, as required by the claimed methods.

The Examiner is reminded that a claim is anticipated only if "each and every limitation is found either expressly or inherently in a single prior art reference." *Celeritas Tech., Ltd. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 47 USPQ 2d 1516 (Fed. Cir. 1998). As discussed above, Talarico *et al.* do not expressly teach the claim limitation requiring that the aPEG be dissolved in solution and then filtered prior to using the aPEG solution to chemically modify hemoglobin.

Moreover, given that many aPEGs are labile in water and, as a result, prior to the present invention aPEGs were typically added to hemoglobin solutions in a powdered form, the claim limitation at issue is also not inherently disclosed by the cited reference. Thus, although Talarico *et al.* teach a method for producing a chemically modified hemoglobin, the reference is not anticipatory because Talarico *et al.* do not teach each and every step of the claimed method. Specifically, the cited reference does not teach a method of producing a chemically modified hemoglobin comprising dissolving an aPEG in a solvent in which it is stable and filtering the resulting aPEG solution prior to combining it with a hemoglobin solution. Therefore, the Examiner has failed to establish a *prima facie* case of anticipation, and the rejection of claims 12-16 and 18 under 35 U.S.C. § 102(b) should be withdrawn.

The Rejection of the Claims Under 35 U.S.C. § 103 Should Be Withdrawn

Claims 12, 17, and 19 were rejected under 35 U.S.C. § 103 as being unpatentable over Talarico *et al.* (2000) *Biochim. Biophys. Acta* 1476: 53-65 in view of Feola *et al.* (U.S. Patent No. 5,439,882). This rejection is respectfully traversed.

As discussed above, Talarico *et al.* disclose a method for producing a PEGylated hemoglobin comprising combining a hemoglobin solution with an aPEG but do not teach using a filtered aPEG solution. Feola *et al.* disclose a composition and method directed to a blood substitute comprising a hemoglobin that is cross-linked intramolecularly with periodate-oxidized ATP (o-ATP) and intermolecularly with periodate-oxidized adenosine (o-adenosine). Feola *et al.* further teach the use of a 0.2 micron Posidyne® filter to remove contaminants from the extracted hemoglobin solution prior to its chemical modification with o-ATP and o-adenosine.

A *prima facie* case of obviousness requires some suggestion to combine the cited references to arrive at the claimed invention and a reasonable expectation of success in such a combination. The claimed invention in the instant case is a method of preparing a chemically modified hemoglobin that is substantially free of contaminants comprising dissolving an aPEG in a solvent in which the aPEG is stabile, filtering the aPEG solution to substantially reduce the level of contaminants, and combining the filtered aPEG solution with a hemoglobin solution. Dependent claim 17, as amended, further comprises filtering the aPEG solution through a 0.2

micron nylon filter. Significant reductions in contaminants present in the chemically modified hemoglobin solution result from using a filtered aPEG solution. See, for example, pages 15-17, Example 4 and Tables 2-3. The Examiner asserts that the motivation to combine the cited references to arrive at the claimed methods arises from the desirability of further removing contaminants from the chemically modified hemoglobin solution of Talarico *et al.* This reasoning is insufficient to establish a motivation to combine the references. Moreover, the references, even if combined, would not allow one of skill in the art to produce the claimed invention.

Talarico *et al.* disclose only a method for producing a chemically modified hemoglobin comprising combining an aPEG with a hemoglobin solution. The reference does not disclose whether the aPEG is combined with the hemoglobin fraction in a powdered form or in solution. Talarico *et al.* do not teach or suggest first dissolving the aPEG in a solvent in which it is stable and then filtering the aPEG solution prior to combining it with the hemoglobin solution, as required by the claimed invention. Prior to the present invention, aPEGs were typically added to the hemoglobin fraction in a powdered form due to their instability in water. The levels of contaminants present in the resulting chemically modified hemoglobin solution are substantially reduced when a filtered aPEG solution is used because powdered aPEG compositions cannot be processed to remove contaminants to the same extent . Furthermore, there is no suggestion in the reference that a stable aPEG solution could be produced, filtered, and successfully used to modify hemoglobin.

Feola *et al.* teach only a method for producing a modified hemoglobin that is crosslinked intramolecularly with o-ATP and intermolecularly with o-adenosine. The cited reference does not teach or suggest the use of an aPEG to chemically modify hemoglobin and, thus, obviously does not suggest using a stable, filtered aPEG solution to modify hemoglobin, as required by the present invention. Thus, given that neither reference teaches or suggests dissolving an aPEG in a solvent in which it is stable and then filtering the aPEG solution to substantially reduce the level of contaminants prior to using it to modify hemoglobin, there is insufficient motivation to combine the cited references to obtain the claimed invention.

Furthermore, although there is insufficient motivation to combine the references, even if combined, the references would not allow one of skill in the art to arrive at the claimed invention. As discussed above, neither reference cited by the Examiner teaches dissolving an aPEG in a solvent and then filtering the aPEG solution, two important steps in the claimed methods. Prior to the present disclosure it was not known that a stable aPEG solution could be produced, filtered, and successfully used to modify a hemoglobin solution. Accordingly, the combination of cited references could not have placed the invention of claims 12, 17, and 19 in the hands of the public, and a *prima facie* case of obviousness under 35 U.S.C. § 103 has not been established.

The Examiner further asserts that claim 17 is obvious in light of the filter taught by Feola *et al.* Dependent claim 17, as amended, further comprises filtering the aPEG solution through a 0.2 micron nylon filter. The cited reference teaches the use of a 0.2 micron Posidyne® filter to remove contaminants from the extracted, unmodified hemoglobin fraction. The Examiner maintains that it would have been obvious to one of skill in the art to use the filter disclosed by Feola *et al.* in conjunction with the method of Talarcio *et al.* to arrive at the method of claim 17. In contrast to claim 17, Feola *et al.* disclose only the use of a 0.2 micron filter to remove contaminants from the extracted hemoglobin solution. As discussed above, Feola *et al.* do not even teach or suggest using an aPEG to chemically modify a hemoglobin solution, and, therefore, do not suggest using any filter to remove contaminants from an aPEG solution. Moreover, the mere fact that Feola *et al.* use a 0.2 micron filter to remove contaminants from a hemoglobin solution is no indication that one of skill in the art would have been motivated to dissolve an aPEG in a solvent in which it is stable, filter the aPEG solution through a filter of any type, and then use the filtered aPEG solution to modify hemoglobin. Therefore, claim 17 is not obvious in view of the cited references.

For the reasons presented above, the Examiner has failed to establish a *prima facie* case of obviousness. Accordingly, Applicants respectfully submit that the claimed methods for producing a chemically modified solution substantially free of contaminants are not obvious in

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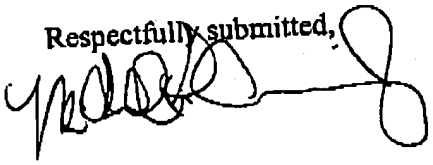
view of the cited references and request that the rejection of claims 12, 17, and 19 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSIONS

The Examiner is respectfully requested to withdraw the rejections and allow claims 12-19. Early notice to this effect is solicited.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,



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Pamela Lockley — October 1, 2003
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